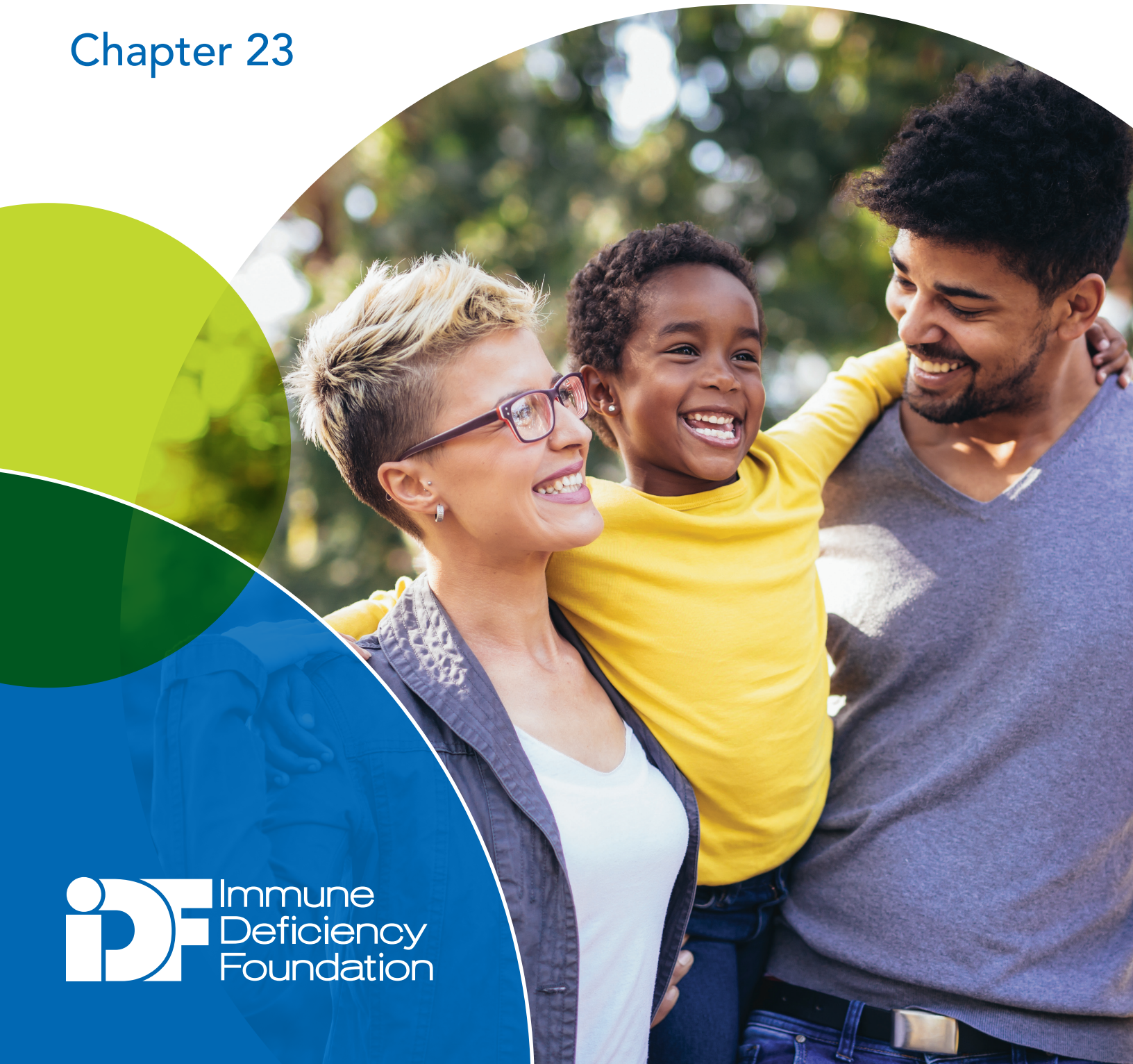
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 23



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Chapter 23

Innate Immune Defects

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Introduction

The immune system is in charge of protecting us from unwelcome invaders. Primary immunodeficiency diseases (PI), in which part of the body's immune system is missing or does not function properly, can be divided into two groups:

1. Those less common conditions with defects in innate immunity, a system of cells and mechanisms that defend the host from infection in a non-specific manner.
2. Those conditions due to defects of adaptive immunity in which defense is carried out in a more specific manner by T cells and antibody producing B cells.

The innate immune system represents our first line of defense. It comprises our physical barriers (such as skin and the mucosa in the gastrointestinal tract, sinuses, and lungs), immune cells (neutrophils, monocytes, macrophages, natural killer cells, and mast cells, among others), and complement proteins. The name innate comes from being naturally present prior to any microbial encounter and for not requiring additional training to do its job.

Innate immune disorders include: Myd88 and IRAK-4 deficiencies, TLR3 deficiency, NF-kappa-B Essential Modulator (NEMO) deficiency syndrome, natural killer (NK) cell deficiency, and defects in interferon-γ (IFN-γ) and interleukin (IL)-12/23 signaling pathways.

Overview

Every time we face a new microbe, several questions need to be addressed in a timely manner. Is it a threat? Is any immediate action required? If yes, of which kind? The innate immune system answers these questions, in a quick and reliable way. Even very specialized cells, like T and B cells, rely on these initial steps to know who the enemy is, when it is time to attack, and what to do.

Innate immune cells deal with the first challenge of identifying which organisms are potentially harmful by using danger sensors known as pattern-recognition receptors (PRRs). These receptors recognize certain structures that are present in pathogens but not in human cells, named pathogen-associated molecular patterns (PAMPs). This way of detecting threats proves to be a very smart strategy. PAMPs are shared by groups of microbes, and they are essential for their survival. This means that a single receptor is able to recognize several pathogens, and, even if mutations occur, the sensing system will remain functional because these structures are so important that they are unlikely to change.

Some of the best-known and widely present PRRs are the Toll-like receptors (TLR) family. In humans, there are 10 different TLRs, termed TLR1 to TLR10. TLR1, -2, -4, -5, -6, and -10 are located on the surface of the cell, where they sense extracellular molecules, while TLR-3, -7,-8, and -9 stay in the cytoplasm inside the cell to recognize intracellular products, such as viral nucleic acids. The binding of certain molecules, like RNA and DNA from viruses to these receptors, initiates a cascade of chemical reactions that will ultimately deliver a message to the nucleus, where genes will be activated to mount an immune response that is appropriate to the type of signal sensed by the TLR.

Innate Immune Deficiencies

Myd88 and IRAK-4 Deficiencies

Several intermediate proteins take part in the process of sending signals sensed by TLRs to the nucleus. Two of these proteins are of importance here, as inherited defects that are known causes of PI.

All TLRs except TLR3 use myeloid differentiation primary response protein 88 (or simply Myd88) as an adaptor (partner) protein. Since Myd88 recruits and interacts with interleukin-1 receptor-associated kinase 4 (IRAK-4) in the signaling pathway, genetic

defects in either Myd88 or IRAK-4 result in the same clinical manifestation of invasive pyogenic infections, which means that pus-inducing bacteria (pyogenic) infect areas that are normally germ free. *Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa* are the most common bacteria to cause infections in these individuals. Infections are usually severe (sepsis, meningitis, arthritis, osteomyelitis, abscesses) particularly during the first years of life. Of note, immune responses to other types of bacteria, viruses, fungi, and parasites are unaffected.

Despite having severe infections, individuals with defects in Myd88 or IRAK 4 commonly present only with low-grade fever and slightly abnormal inflammatory markers like a sedimentation rate or CRP. Diagnosing these defects can be tricky as most routine immunological tests are normal. Some individuals show abnormal antibody responses to polysaccharide antigens and elevated serum levels of IgE. Specialized laboratories can run specific tests to evaluate TLR function, but a definitive diagnosis relies on gene sequencing.

Infection severity for these individuals decreases with age, once other arms of the immune system mature and take control of the troublesome pathogens. However, early-life infections can be life threatening and require careful management. Caregivers and healthcare professionals must be prepared to provide immediate and aggressive treatment to infections, in spite of mild symptoms. Most of these individuals benefit from prophylactic antibiotics, and some individuals might need immunoglobulin (Ig) replacement therapy temporarily.

TLR3 Deficiency

Individuals with defective TLR3, the only TLR that does not signal through Myd88, are at increased risk of developing herpes simplex virus (HSV-1) encephalitis, a severe viral infection of the brain and central nervous system. It typically occurs in childhood, when individuals first encounter this virus (HSV-1 is the most common cause of cold sores). Infection susceptibility is restricted to HSV-1, as individuals are able to mount effective responses against other viruses, bacteria, and fungi. HSV-1 encephalitis is a rare infection and should prompt investigation for immunodeficiency. Other genes related to TLR3 signaling, such as *UNC93B1, TRIF, TRAF*, and *TBK1*, also need to be screened. Mortality rates associated with these diseases are high (around 70%) when they are untreated. However, outcomes can improve with the use of antivirals, interferons, and supportive care.

NEMO Deficiency Syndrome

In the chain of chemical reactions after TLR activation, NF-kappa-B Essential Modulator (NEMO) is an important protein downstream of Myd88 and IRAK-4. NEMO is required for the activation of the NF-kappa-B family of transcription factors. These factors ultimately regulate lymphocyte development and proliferation, inflammation, and immune responses.

Besides TLRs, other signaling pathways also recruit NEMO. For this reason, in NEMO deficiency, many cellular processes are affected and individuals tend to have more clinical manifestations compared to TLR deficiencies. One of these pathways starts with the ectodysplasin-A receptor, which is important for the development of ectodermal tissues, such as hair, skin, nails, etc. Malfunction of this pathway results in anhidrotic ectodermal dysplasia (EDA), a condition characterized by dry and thickened skin, conical teeth, absence of sweat glands, and thin, sparse hair. Several different defects can cause EDA, but the association of EDA and immune defects (EDA-ID) is highly suggestive of NEMO deficiency.

From the immunological standpoint, individuals with NEMO deficiency syndrome have a range of infections with pyogenic organisms. *Streptococcus pneumonia and Staphylococcus aureus* are the most common pathogens, but individuals with NEMO can also have viral and fungal infections. Infections can be severe and may be found virtually anywhere in the body, including the lungs, skin, central nervous system, liver, abdomen, urinary tract, bones and gastrointestinal tract. Many individuals have humoral immunity problems with a complete lack of antibody response against certain bacteria, such as pneumococcus, despite vaccination. A subset of these individuals presents with high serum levels of IgM. Other individuals exhibit defects in additional arms of the immune system that cause increased susceptibility to mycobacteria. These individuals may develop disseminated infection if they receive BCG (the live vaccine against tuberculosis, which is commonly given in countries other than the U.S.).

About 90% of individuals with NEMO deficiency have EDA. A small group of individuals have a more severe disease course presenting with two additional conditions: osteopetrosis (a disorder in which bones are denser, prone to fractures and the bone marrow fails to produce blood cells) and lymphedema (fluid retention due to defects in lymphatic vessels), known as OL-EDA-ID syndrome.

NEMO deficiency is inherited in an X-linked manner; hence, almost all cases occur in boys. Female carriers are normally free of immune symptoms, but some might have a condition called incontinentia pigmenti, mostly affecting the skin.

Diagnosis of NEMO deficiency is based on clinical manifestations. The presence of EDA is usually a hint but can be absent in 10% of the individuals. Almost all individuals with NEMO deficiency lack protective levels of pneumococcal antibodies following pneumococcal vaccination. Routine immunological tests are variable among individuals, and normal results do not rule out the diagnosis. Diagnostic confirmation requires genetic testing.

Therapy for NEMO deficiency is aimed at preventing infections and complications stemming from infection. Individuals with antibody defects receive Ig replacement therapy. While this therapy is a cornerstone of treatment, it is insufficient alone to control infections given the broad-based immune defects in these individuals. Therefore, individuals also receive a series of prophylactic antibiotics as part of their infection preventive regimen.

Individuals with NEMO deficiency should see their primary care physician and immunologist regularly as problems and complications can be frequent. Treatment should be started promptly whenever an infection is suspected. Hematopoietic stem cell transplantation (HSCT) has been used for some individuals with NEMO deficiency. Outcomes after transplantation have been variable. Transplantation is able to correct the immunological defects of NEMO deficiency but does not improve the other complications of the syndrome.

Natural Killer (NK) Cell Deficiency

NK cells are innate immune cells important in the killing of cancer cells or cells that have been infected by viruses. NK cells are so named because they are able to kill cells without the need of any pre-training. They are present in relatively low numbers in the bloodstream and in tissues.

NK cells kill virus-infected cells by poking holes on the cells' membranes and injecting toxic proteins into the viral infected cells. NK cells are particularly important in the defense against herpes viruses. This family of viruses includes herpes simplex virus (HSV) that causes cold sores and genital herpes; Epstein-Barr virus (EBV) that causes infectious mononucleosis; cytomegalovirus (CMV); and varicella-zoster virus (VZV) the cause of chicken pox and shingles. Individuals with NK cell deficiency present with severe or recurrent infections caused by herpes viruses and papilloma viruses that can cause warts and cancer.

Human NK cell deficiencies have been divided into two categories:

1. Quantitative defects: with absent or very low numbers of NK cells in the peripheral blood
2. Qualitative defects: with normal numbers of NK cells but abnormal NK cell function

NK cell deficiencies in the first category have been labeled as classical NK cell deficiencies and those in the second functional NK cell deficiencies.

Diagnosis includes quantification of NK cells, as well as assessment of function (ability to kill target cells). Several medications and disease processes may have an impact on NK cell numbers and activity. Therefore, abnormal tests should be repeated on separate occasions to establish the diagnosis. Genetic causes of NK cell deficiency have been identified including autosomal recessive and dominant forms.

Vaccination against human papillomavirus (HPV) is recommended. Some individuals might need continuous use of antiviral agents and may benefit from Ig replacement therapy. More specific therapies are under study. For individuals with severe disease, HSCT might be considered.

Defects in Interferon-γ (IFN-γ) and Interleukin (IL)-12/23 Signaling Pathways

Macrophages ("big eaters" in Greek) are innate immune cells found in all human tissues. They are able to kill microbes by eating and subsequently digesting them. However, some pathogens, such as *Mycobacteria* and *Salmonella*, learned how to escape from destruction and became capable of surviving and growing within macrophages. To overcome this, macrophages produce IL-12 to activate specialized T and NK cells and stimulate interferon-γ (IFN-γ) production that will act on macrophages leading to the killing of intracellular microbes. This cooperation represents the IFN-γ/IL-12 pathway. Rare genetic defects affecting this pathway have been described and are collectively called Mendelian susceptibility to mycobacterial disease (MSMD).

The hallmark of MSMD is susceptibility to mycobacteria (the family of bacteria that causes tuberculosis and related infections) and salmonella infections, with some individuals also suffering from viral, fungal, and parasitic infections. Many of the affected individuals become ill in infancy after

receiving the live anti-tuberculosis BCG vaccine. Other individuals have skin infections, swollen lymph nodes or blood stream infections later in life, upon encountering *Mycobacterium tuberculosis* or other environmental nontuberculous mycobacteria (NTM) that are not harmful to healthy individuals.

In about half of the cases, the genetic cause of MSMD is not known. Some individuals presenting with adult-onset infections resembling MSMD do not have genetic defects in the IFN-γ/IL-12 pathway but rather have autoantibodies directed against interferon-γ.

Once MSMD is suspected, diagnosis can be sought by investigating whether the components (proteins) involved in the IFN-γ/IL-12 pathway are present and/or functionally adequate. For that reason, sometimes, specific tests to assess function are needed. Genetic testing can confirm the diagnosis.

Individuals with MSMD should not receive BCG or live Salmonella vaccines, as complications can be life threatening. Treatment of infections consists of prolonged courses of antibiotics, and surgical procedures are sometimes required. Depending on their defect, IFN-γ replacement can benefit some, but not all individuals with MSMD. Once infections are cleared, prophylactic antibiotics are usually prescribed. HSCT is restricted to severe cases, given that rejection rates after transplant in these individuals are high.

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